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**Title: A Randomized Controlled Trial of Lifestyle Modification and Lorcaserin for Weight Loss Maintenance**

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## 1. STUDY OBJECTIVE

To evaluate, in a 52-week randomized, double-blind, placebo-controlled trial, the efficacy of lorcaserin (10 mg BID) in maintaining a loss of 5% or more of initial weight, achieved during a prior 14-week group lifestyle modification program.

## 2. BACKGROUND

### 2.1 The Problem of Obesity

Obesity, defined by a BMI  $\geq 30$  kg/m<sup>2</sup>, is the most common nutritional disease in the United States, affecting about 36% of adults age 20 years and over. An additional 33% of American adults are overweight, as judged by a BMI of 25.0-29.9 kg/m<sup>2</sup>. Obesity is associated with a number of co-morbidities including type 2 diabetes (70% of people with type 2 diabetes are obese) and cardiovascular disease. Losing as little as 5% of initial weight improves co-morbid conditions including insulin resistance, dyslipidemia, and hypertension.

A program of diet, physical activity and behavioral therapy is the first line treatment for obesity. This approach produces significant weight loss ( $\geq 5\%$ ) but is often followed by weight gain. Patients regain about 35% of their initial weight loss in the first year and 50% or more have

returned to their baseline weight by 5 yr. It is therefore, highly desirable to identify effective interventions, which would improve long-term maintenance of prior weight loss.

## 2.2 Benefits of Weight loss

A 5–10% reduction in body weight in obese individuals improves several risk factors for cardiovascular disease (CVD) including blood pressure, triglyceride levels, low-density-lipoprotein cholesterol, blood glucose, and sleep apnea.<sup>1-3</sup> The Diabetes Prevention Program (DPP) revealed that a 7% reduction in initial weight, combined with 150 minutes of activity, reduced the risk of developing type 2 diabetes by 58%, compared with placebo, in at-risk overweight/obese individuals at an average of 2.8 years follow-up.<sup>4</sup> Losses  $\geq 10\%$  are associated with greater improvements in CVD risk factors<sup>5</sup> and are more consistent with obese individuals' desired weight loss goals.<sup>6</sup>

## 2.3 Current Status of Lifestyle Modification for Obesity

Lifestyle modification is the cornerstone of treatment for most obese individuals, as recommended by the NHLBI's Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults.<sup>7</sup> In trials conducted in academic medical centers, persons treated by a 1200-1500 kcal/d diet, combined with regular exercise and a comprehensive program of group or individual lifestyle modification, lose approximately 7-10% of initial weight in 20-26 weeks.<sup>4,7,8</sup> Lifestyle modification has been incorporated in popular commercial programs such as Weight Watchers,<sup>9,10</sup> which was found in a randomized trial to induce a loss of 5.3% of initial weight in the first 26 weeks (and 3.3% at year 2).<sup>10</sup> Diet and exercise interventions are increasingly delivered by Internet,<sup>11,12</sup> the most effective program which induced a loss of 5.5% of initial weight in 6 months.<sup>12</sup> The reduced efficacy of lifestyle modification in these two cases, as compared with when delivered at academic medical centers, is probably attributable to the use of large group sessions (50 or more people) which limit individual attention (i.e., Weight Watchers) and to the lack of frequent, personalized feedback from a trained interventionist (i.e., Internet programs). The use of telephone-delivered lifestyle counseling produces weight losses that are roughly equal to those achieved in face-to-face meetings,<sup>13-15</sup> suggesting the promise of the former approach.

## 2.4 Improving the Non-Surgical Treatment of Obesity

### 2.4.1 Increasing initial weight losses

Investigators currently are examining methods to increase initial weight losses and, thus, achieve greater improvements in CVD risk factors. The use of portion-controlled servings of conventional foods,<sup>16</sup> as well as liquid meal replacements,<sup>3,17</sup> is effective in increasing initial weight losses by approximately 3 to 5 percentage points, as compared with the prescription of a self-selected diet of conventional foods with the same calorie goal. Portion-controlled servings, by providing foods of pre-determined quantity and energy content, reduce obese individuals'

tendency to underestimate their calorie intake, which has been found to be as great as 40% when a self-selected diet of conventional foods is consumed.<sup>18,19</sup> The use of liquid meal replacements and snack bars contributed to the 8.6% reduction in initial weight achieved in the first year of the Look AHEAD study.<sup>20</sup>

The addition of pharmacotherapy to lifestyle modification also increases initial weight loss, by approximately 3 to 7 percentage points compared with lifestyle modification alone. This additive benefit is observed whether participants receive a modest program of lifestyle modification (e.g., one or two visits with an interventionist)<sup>21</sup> or a comprehensive program (i.e., weekly group meetings).<sup>22,23</sup> Current medications approved by FDA for chronic weight management include orlistat (a gastric and pancreatic lipase inhibitor),<sup>24,25</sup> lorcaserin (a selective serotonin agonist),<sup>26</sup> and the combination of phentermine and topiramate (a serotonin and dopamine reuptake inhibitor, combined with a medication for epilepsy/seizure).<sup>21,27</sup>

#### 2.4.2 Improving the maintenance of lost weight

Weight regain remains the Achilles' heel of behavioral treatment.<sup>8,18</sup> Obese adults, on average, regain one-third of their weight loss in the year following treatment, with increasing regain over time.<sup>8</sup> Two approaches facilitate the maintenance of lost weight. Lifestyle counseling, on a twice-monthly or monthly basis, improves weight maintenance for up to 2.5 years compared with no further treatment.<sup>28,29</sup> Pharmacological treatment offers another option. Several studies have revealed significantly better weight-loss maintenance at 1 or more years in individuals who were randomly assigned, following initial weight loss, to receive weight-loss medication versus placebo.<sup>24,26,30-32</sup> FDA-approved weight loss medications are an option for individuals with a BMI  $\geq 30$  kg/m<sup>2</sup> or persons with a BMI  $\geq 27$  kg/m<sup>2</sup> with a weight-related co-morbidity (e.g., type 2 diabetes, hypertension, etc.).

#### 2.4.3 Lorcaserin

Lorcaserin (Belviq<sup>TM</sup>) is a selective serotonin 2C receptor agonist that improves the management of obesity. A randomized, controlled trial compared two doses of lorcaserin (10 mg BID vs 10 mg QD) with placebo, all of which were combined with moderate intensity lifestyle counseling.<sup>33</sup> Significantly more participants in the lorcaserin BID and QD groups lost  $\geq 5\%$  of initial weight than with placebo (47.2%, 40.2, and 25.0%, respectively). A second trial that compared lorcaserin (10 mg BID) and placebo (both with lifestyle counseling) observed 1-year mean (SEM) weight losses of  $5.8 \pm 0.2\%$  and  $2.2 \pm 0.1\%$  of initial weight, respectively.<sup>26</sup> Significantly more participants treated by lorcaserin than placebo lost 5% or more of initial weight (47.5% vs 20.3%), as well as 10% or more (22.6% vs 7.7%).<sup>3</sup>

Lorcaserin clearly is effective in inducing weight loss. However, it could prove to be even more beneficial in facilitating the maintenance of lost weight, by far the greater challenge in weight management. Studies of both sibutramine (10-15 mg/d)<sup>30</sup> and liraglutide (3.0 mg/d)<sup>34</sup> showed that following the loss of approximately 6%-7% of initial weight, achieved with lifestyle modification (i.e., diet run-in), the subsequent addition of medication increased weight loss by an additional 5%-6% over 12 months. With both medications, long-term weight loss was superior in patients who received medication (plus lifestyle intervention) than placebo (with lifestyle

intervention). Sibutramine is no longer available for the treatment of obesity (because of its association with cardiovascular disease) and liraglutide 3.0 mg is not approved for the management of obesity at this time. Orlistat, while superior to placebo, was not effective in facilitating the maintenance of lost weight achieved during a diet run-in period.<sup>32</sup> Neither the efficacy of lorcaserin nor the phentermine-topiramate combination has been tested for facilitating the maintenance of lost weight, achieved with a prior group lifestyle modification program. In a previously discussed study,<sup>26</sup> participants who received lorcaserin and lost 5% or more of initial weight at 1 year, were more likely to maintain the 5% loss at year 2 if they had been re-randomized to lorcaserin rather than to placebo at the end of year 1. Sixty-eight percent of participants who remained on lorcaserin for the second year maintained the 5% loss, compared with 50% of those who were randomized after 1 year to placebo.<sup>26</sup> The goal of the present study is to maintain larger long-term weight losses by inducing larger initial losses with the group lifestyle modification program.

### 3. SPECIFIC AIMS

#### 3.1 Primary Objective

The primary objective is to assess the efficacy of lorcaserin (with lifestyle intervention), compared with placebo (with lifestyle intervention) in facilitating the maintenance of prior weight loss achieved during a 14-week group lifestyle modification program. The efficacy of lorcaserin will be measured by change in weight (kg) from randomization to week 52. The co-primary outcome will compare the percentage of participants assigned to lorcaserin vs placebo who maintained the loss of 5% or more of initial weight, achieved during the 14-week dietary run-in period.

#### 3.2 Hypotheses

We hypothesize that at 52 weeks post randomization the group assigned to lorcaserin will achieve significantly better maintenance of the prior 5% weight loss than will the placebo-treated group.

#### 3.3 Primary End Point

The primary end point is the maintenance of weight loss (previously achieved during the 14-week lifestyle modification program), as defined by change in weight (kg) from randomization to week 52. The co-primary end-point is the percentage of participants in each group that maintain the full 5% weight loss, achieved in the 14-week prior group lifestyle modification program.

#### 3.4 Secondary Endpoints

Secondary endpoints include percentage change in body weight from randomization to week 52, as well the portion of participants in the two groups who achieve an additional loss  $\geq 5\%$  of body weight, as measured from randomization. The two groups also will be compared on changes (from randomization to week 52) in cardiometabolic risk factors (including waist circumference, systolic and diastolic blood pressure, triglyceride values, LDL and HDL cholesterol, glucose,

insulin, and high sensitivity C-reactive protein), quality of life (as measured by the Short Form Health Survey [SF-36] and the Impact of Weight on Quality of Life-Lite [IWQOL]), appetite control (as measured by the Eating Inventory, visual analogue scales, the Eating Disorder Examination-Questionnaire, and the Yale Food Addiction Scale), frequency with which certain foods are eaten (as measured by the Block Food Frequency Questionnaire, and physical activity will be assessed by the Paffenbarger Physical Activity Survey.

The proportion of participants who maintain losses  $\geq 10\%$  and  $\geq 15\%$  of initial weight, as measured from the start of the 14-week group lifestyle modification program, also will be compared.

## 4. STUDY DESIGN

### 4.1 General Design

This is a 52 week, double blind, placebo controlled, parallel group design trial that will enroll overweight/obese participants who achieved a  $\geq 5\%$  weight loss in a prior 14-week group lifestyle modification program. The total duration of the study will be 70 weeks (which includes a final medical visit at 56 weeks post-randomization to assess participants' health 4 weeks after the trial and study medications have been stopped).

A total of 182 obese men and women (body mass index [BMI]  $\geq 33$  and  $\leq 55$  kg/m<sup>2</sup> or BMI  $\geq 30$  kg/m<sup>2</sup> with an obesity-related comorbidity) will be enrolled in a 14-week group lifestyle modification program (offered at the University of Pennsylvania's Center for Weight and Eating Disorders), of whom  $\geq 136$  (75%) are expected to lose  $\geq 5\%$  of initial weight and will be eligible for randomization to lorcaserin (with lifestyle intervention; N=68) or placebo (with lifestyle intervention; N=68). (Note: A portion of the lifestyle intervention program will be provided remotely by conference call)

#### Other Therapy:

Participants will be expected to use medications (prescribed by their primary care providers) to control traditional cardiometabolic risk factors (e.g., hypertension, hypercholesterolemia, etc) and other co-morbid conditions, with the exception of medications listed below under "exclusions." In all cases, the subjects' primary care provider (PCP) will be asked at the study's outset to keep medication constant throughout the study, whenever possible. Participants will be expected to have been on their medication regimen (including the dose) for 3 months prior to entering the dietary group lifestyle modification program.

## 5. SUBJECT SELECTION

### 5.1 Subject Recruitment

Participants will be recruited from advertisements in local media outlets (newspapers, radio), as well as flyers posted at the University. We also will advertise the study to health care providers who work in Penn's Clinical Care Associate practices, with whom we have collaborated previously.<sup>35</sup>

## 5.2 Inclusion/Exclusion Criteria

Key Inclusion Criteria to enter the 14-week group-lifestyle modification program:

1. BMI  $\geq 33$  kg/m<sup>2</sup> and  $\leq 55$  kg/m<sup>2</sup> (or  $\geq 30$  kg/m<sup>2</sup> with an obesity-related comorbidity)
2. Age  $\geq 21$  years and  $\leq 65$
3. Eligible female patients will be:
  - non-pregnant, evidenced by a negative urine dipstick pregnancy test
  - non-lactating
  - surgically sterile or postmenopausal, or they will agree to continue to use an accepted method of birth control during the studyAcceptable methods of birth control are: hormonal contraceptives; double barrier method (condom with spermicide or diaphragm with spermicide); intrauterine device; surgical sterility; abstinence; and/or postmenopausal status (defined as at least 2 years without menses).
4. Participants must:
  - have a PCP who is responsible for providing routine care
  - have reliable telephone service with which to participate in conference calls
  - understand and be willing to comply with all study-related procedures and agree to participate in the study by giving written informed consent

Key Exclusion Criteria:

1. Pregnant or nursing (or plans to become pregnant in the next 18 months)
2. Current major depressive episode, active suicidal ideation, or history of suicide attempts
3. Use in the past 14 days of monoamine oxidase inhibitors, SSRI, SNRI, tricyclics, lithium, triptans, antipsychotics, cabergoline, linezolid, tramadol, dextromethorphan, tryptophan, bupropion, St. John's Wort, or medicines to treat erectile dysfunction
4. Uncontrolled hypertension (systolic blood pressure  $\geq 160$  mm Hg, or diastolic blood pressure  $\geq 100$  mm Hg)
5. Type 1 diabetes or type 2 diabetes
6. A fasting glucose  $\geq 126$  mg/dl or HbA1c  $\geq 6.5$
7. Recent history of cardiovascular disease (e.g., myocardial infarction or stroke within the past 6 months), congestive heart failure, or heart block greater than first degree
8. Clinically significant hepatic or renal disease
9. Thyroid disease not controlled
10. History of malignancy (except for non-melanoma skin cancer). (Applicants, however, who have been free of disease for 5 years or more are potentially eligible.)
11. Severe valvular heart disease (i.e., stage c, as defined by 2014 AHA/ACC guidelines)
12. Use of medications known to induce significant weight loss/gain, including chronic use of oral steroids

13. Psychiatric hospitalization within the past 6 months
14. Self-reported alcohol or substance abuse within the past 12 months, including at-risk drinking (current consumption of  $\geq 14$  alcoholic drinks per week)
15. Loss of  $\geq 10$  lb of body weight within the past 3 months
16. History of (or plans for) bariatric surgery
17. Inability to walk 5 blocks comfortably or engage in some other form of aerobic activity (e.g., swimming)
18. Any serious or unstable medical or psychological condition that, in the opinion of the investigator, would compromise the patient's safety or successful participation in the study

Key Inclusion Criteria to be randomized to the 52-week weight loss maintenance study:

1. Participants must have lost  $\geq 5\%$  of initial weight in the group lifestyle modification program
2. Participants must have a BMI  $\geq 30$  and  $\leq 55$  kg/m<sup>2</sup> or have a BMI  $\geq 27$  kg/m<sup>2</sup> with a obesity-related co-morbid condition
3. All other inclusion/exclusion criteria from the 14-week group lifestyle modification program apply for participants in the 52-week weight loss maintenance study.

## 6. STUDY PROCEDURES

### 6.1 Screening Procedures

All applicants will be screened by phone to determine whether they potentially meet eligibility criteria. We will obtain a waiver of written documentation of consent for the telephone screen. Those who remain interested in the trial will be scheduled for an in-person interview. The Weight and Lifestyle Inventory (WALI),<sup>36</sup> a paper-and-pencil inventory that assesses general eating and lifestyle behaviors and the Beck Depression Inventory (BDI) will be mailed to eligible participants following the phone screen and completed by them prior to their screening/informed consent visit. (All patients and subjects at our Center complete the WALI and BDI to facilitate their initial interview.) The in-person interview will be conducted by a psychologist, who will obtain informed consent and evaluate participants' behavioral eligibility (i.e., willingness and appropriateness to participate). This will include our assessment of the applicant's mood (as measured by interview and the BDI) and suicidality (including history of suicidal ideation and behavior, as assessed at screening by interview and the Columbia-Suicide Severity Rating Scale).

Participants who remain interested and pass this portion of the assessment will proceed to meet with the study's nurse practitioner or physician, who will obtain a medical history and conduct a physical examination to determine medical eligibility. Persons who continue to remain eligible will proceed to have an electrocardiogram (EKG) and fasting blood test to determine that final eligibility criteria are met. Safety screening labs will include a complete blood count (CBC), comprehensive metabolic panel (CMP), lipid panel, hemoglobin A1c, insulin, high sensitivity C-reactive protein (hs-CRP), a thyroid-stimulating hormone (TSH) for subjects with a history of thyroid disorder, and a urine pregnancy test (for females of child-bearing age).

### 6.2 Study Visits

**Screening visit.** The following procedures will be completed at the screening visit as discussed above: informed consent, medical history, weight, height, waist circumference measurement, blood draw, urinalysis, review of medication, full physical exam, electrocardiogram, sitting blood pressure and pulse rate, and meeting with psychologist whose assessment will be used as a part of determining the subject's eligibility for the study.

**Phase 1: 14-Week Group Lifestyle Modification Program.** All participants will complete an initial 14-week group lifestyle modification program, designed to induce a loss  $\geq 5\%$  of initial weight. They will attend weekly group weight loss sessions (of 90 minutes, with 10 to 12 participants), led by registered dietitians (RDs) or behavioral psychologists. At week 1, they will be instructed to consume their usual diet and to record their food intake (i.e., all foods and beverages consumed). From weeks 2 to 13, they will be instructed to consume a 1000-1200 kcal/d diet that provides four servings daily of a liquid shake (Health Management Resources – HMR; 160 kcal per shake), an evening meal comprised of a frozen food entrée (250-300 kcal), with a serving of fruit and a salad. Another serving of fruit will be permitted after dinner, providing a diet of approximately 1000-1200 kcal/day. All HMR products will be provided free of charge. Participants will be responsible for purchasing frozen food entrees and other foods. Beginning at week 6, participants will be encouraged to gradually increase their physical activity from a minimum of 30 minutes/week (at week 5) to 175 minutes/week at week 14. From weeks 12-14, participants will be prescribed a re-feeding diet that gradually replaces the consumption of shakes with conventional foods, so that they use of shakes will be terminated by week 14. Participants will be scheduled for their randomization visit (following a last group session) to determine that they have lost 5% or more of initial weight and meet BMI and other study criteria for randomization (as determined by a follow up physical examination and other tests). For candidates with an obesity-related co-morbidity (e.g., hypertension, hypercholesterolemia, sleep apnea, osteoarthritis, etc.), participants will be informed that they will not be able to participate in the randomized controlled trial, if they fall below a BMI of  $27 \text{ kg/m}^2$  during the prior group lifestyle modification program. They will be informed when they have reached a BMI of  $27.5 \text{ kg/m}^2$  and encouraged to slow their rate of weight loss so that they do not reduce below a BMI of  $27 \text{ kg/m}^2$ . Falling below a BMI of  $27 \text{ kg/m}^2$  will make them ineligible to participate in the randomized controlled trial of lorcaserin. Participants will be informed that they may resume active weight loss once the randomized controlled trial has begun. Similar steps will be taken with individuals who are free of obesity-related co-morbidities and reach a BMI of  $30.5 \text{ kg/m}^2$  during the group behavioral weight loss program. Persons who do not have an obesity-related co-morbidity must have a BMI  $> 30 \text{ kg/m}^2$  to receive prescription weight loss medication. Persons who fail to meet appropriate BMI criteria at the outset of the randomized controlled trial will not be permitted to participate.

All group sessions during the Phase I group lifestyle modification program will be conducted at the University of Pennsylvania's Center for Weight and Eating Disorders, following a protocol adapted from the Look AHEAD study (developed by Dr. Wadden and colleagues).

### **Phase 1 Medical Monitoring**

**Medical screening visit.** As discussed previously, persons who are interested in the study will undergo a complete physical examination at which height, weight, and blood pressure will be



measured. An EKG will be obtained, as well as a fasting blood test that will include CBC, CMP, lipid panel, insulin, hs-CRP, and hemoglobin A<sub>1c</sub>. For subjects with a history of thyroid disorders, a measurement of TSH will be added. For women of childbearing potential, a urine pregnancy test will also be performed. Results of these tests will be reviewed by the study physician/nurse practitioner to determine whether the participant has any contraindications to weight loss or to the use of lorcaserin. These contraindications include but are not limited to: any major active kidney, liver, cardiovascular, or cerebrovascular disease; blood pressure  $\geq$  160/100 mm Hg; or the use of any medications that significantly affect weight (weight loss or weight gain).

**Ongoing medical visits and safety measures.** During the 14-week group lifestyle modification program, vital signs (blood pressure and pulse) will be measured at weeks 1, 2, 4, 6, 8, 10, 12, and 14. At week 8 a fasting blood test will be repeated and will include a CBC and CMP. Women who are capable of becoming pregnant will undergo another urine pregnancy test at this time. In addition, participants will have a brief medical visit (10 minutes) with the study physician/nurse practitioner to check for possible complications of early weight loss. Mood will be assessed by verbal report throughout the 14-week program. Participants who report significant depression or emotional distress will be referred to their primary care provider for further evaluation.

**Phase 2: 52-Week Weight Loss Maintenance Program.** Following randomization to medication conditions, all participants will attend group lifestyle sessions, designed to facilitate the maintenance of the 5% or greater weight loss achieved during the run-in period. Group sessions (10-12 participants) will last 90 minutes and will be offered at post-randomization weeks 2, 4, 6, 8, 10, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52. The first two group sessions (weeks 2 and 4) will be held in person (on site), after which sessions will alternate between on-site visits and conference calls. Telephone delivered lifestyle counseling has been shown to be as effective as on-site counseling and is more convenient to participants. All participants will have an individual visit with their interventionist at their randomization visit. All treatment sessions for the 52-week weight loss maintenance program will be delivered following a modified version of the Look AHEAD study.

All participants will be instructed to consume a self-selected diet of conventional foods, consistent with their food preferences. Those who weigh < 250 lb will be prescribed 1500-1700 kcal/day, while those >250 lb will be prescribed 1800-2000 kcal/day. These calorie values are consistent with those reported by participants in the National Weight Control Registry. These calorie targets are lower than those that would be achieved by subtracting 500-600 kcal from patients' estimated energy requirements and are designed to compensate for obese individuals' underestimation of intake by approximately 40% (as judged by comparison to doubly labeled water). Participants will be counseled on how to consume a well-balanced diet and will use a calorie counter (provided to them) to meet their calorie targets.

Participants will be instructed in a program of behavioral skills designed to prevent weight regain (as delivered by the Look AHEAD study). This will include encouraging participants to increase their physical activity to  $\geq$ 200 minutes per week (principally through walking or other aerobic activity).

## Phase 2 Medical Monitoring

Following the 14-week group lifestyle modification program and immediately prior to randomization (to lorcaserin or placebo), participants will complete a second brief history and physical examination and undergo another EKG. The study physician/nurse practitioner will again confirm that the participant does not have any contraindications to weight loss or to the use of lorcaserin. A blood test (which will include a CBC, CMP, lipids, insulin, hs-CRP and hemoglobin A<sub>1c</sub>) and urine pregnancy test (for women of childbearing potential) will be repeated at this time.

Following randomization (to lorcaserin or placebo), vital signs (blood pressure and pulse) will be measured at weeks 2, 4, 8, 12, 20, 24, 28, 36, 44, and 52. A blood test (which will include a CBC, CMP, lipids, insulin, hs-CRP and hemoglobin A<sub>1c</sub>) and urine pregnancy test (for women of childbearing potential) will be repeated at weeks 12, 24, 36 and 52. Participants will attend brief medical visits (10 minutes) with the study physician/nurse practitioner at weeks 2, 4, 8, 12, 24, 36, and 52, with a final visit at week 56 for health assessment after terminating medication at week 52. At each medical visit, participant's response to the medication will be assessed. Study subjects will be asked whether there has been any change in their health or medications. They also will be asked about their mood or any thoughts of harming themselves through administration of the Columbia-Suicide Severity Rating Scale (C-SSRS). In the event of mental health events, participants will be referred to the study's psychologist or psychiatrist for further evaluation, if required. For all non-study-related medical events, participants will be referred to their own primary care provider.

## 6.3 Outcome Measures

**Primary outcome measure: body weight.** Two co-primary endpoints will be tested at week 52: 1) change in body weight (in kg) as measured from randomization to week 52; and 2) the percentage of participants in the two groups that (at week 52) maintained the  $\geq 5\%$  reduction in body weight achieved during the 14-week group lifestyle modification program.

**Body weight** will be measured at all clinic visits. However, for purposes of the primary outcome, weight will be assessed: at screening (week -14, prior to the group lifestyle modification program); at randomization; and at weeks 24 and 52. Weight will be measured on a digital scale (to the nearest 0.1 kg) with participants dressed in light clothing, without shoes. Two measurements will be taken on each occasion.

**Cardiometabolic risk factors** will be assessed at screening (week -14, prior to group lifestyle modification program); randomization; and weeks 24 and 52. Fasting blood samples (i.e., following an overnight fast) will be drawn on each occasion and assayed for CMP, CBC, lipid panel, , insulin, hs-CRP and hemoglobin A<sub>1c</sub>. (Samples will be analyzed by Quest Diagnostics.) Blood pressure and pulse will be measured on each occasion using an automated monitor (Dinamap, model 9300). Two readings will be taken on each occasion (at 1-minute intervals), after participants have been seated for at least 5 minutes. Waist circumference (measured horizontally halfway between the lowest rib and the top of the hipbone) to the nearest 0.1 cm will

be assessed on the same schedule. Two waist measurements will be obtained at each assessment visit.

**Mood, quality of life, weight bias, eating behavior, sleep, stress/fatigue, and physical activity.** Mood will be assessed on the same schedule as the primary outcome using the PHQ-9 and at each medical visit using the C-SSRS. Quality of life will be assessed on the same schedule as the primary outcome using SF-36 and IWQOL-Lite. The experience of weight bias will be evaluated by the Weight Bias Internalization Scale, the Experiences of Weight Bias questions, the Stigmatizing Situations Inventory, the Causal Attributes for Obesity scale, and the Everyday Discrimination Scale. Cognitive restraint, disinhibition, and hunger will be evaluated at the same time, using the Eating Inventory (EI) and visual analogue scales. Binge eating will be assessed by the Eating Disorder Examination-Questionnaire (EDE-Q). Food addiction will be measured using the Yale Food Addiction Scale, food cravings by the Food Craving Scale, and stress-related eating by the Eating and Appraisal Due to Emotions and Stress Questionnaire. Mindfulness while eating will be assessed by the Mindful Eating Questionnaire and the Philadelphia Mindfulness Questionnaire. Stress will be assessed by the Perceived Stress Questionnaire, fatigue by the Fatigue-Short Form, and sleep by the Pittsburgh Sleep Quality Index and Berlin Sleep Questionnaire. Physical activity will be assessed by the Paffenbarger Physical Activity Survey. The third cohort of participants will have the option of completing the Experiences of Weight Bias questions, Weight Bias Internalization Scale, and Causal Attributions for Obesity Scale a second time 1 week after the initial administration to assess the test-retest reliability of these measures.

Safety Measures:

### **Phase 1 Risks**

The risk of adverse medical or psychiatric events should be minimized by the careful screening procedures to be used. The principal risks during the group lifestyle modification program include:

**Hypoglycemia.** Hypoglycemia may occur during periods of calorie restriction and weight loss. Participants will be instructed what to do if they experience symptoms of hypoglycemia.

**Risk of gallstones.** Rapid weight loss may increase the risk of gallstones. The risk of gallbladder disease will be reduced by limiting weight loss to no more than 3 pounds per week for 3 consecutive weeks.

**Blood draw.** Risks of drawing blood include pain, bruising at the puncture site, swelling, feeling faint or lightheaded, and rarely infection.

### **Phase 2 Risks**

The risks associated with the use of lorcaserin will be minimized by re-screening participants prior to randomization and by the inclusion of 7 brief medical visits during the 52-week study. Subjects will be asked at each medical visit if they have experienced any changes in their health. The principal risks associated with lorcaserin include:

**Serotonin syndrome.** Study participants will be instructed to avoid taking other serotonergic drugs to avoid the occurrence of this adverse event. Treatment with lorcaserin will be immediately discontinued if a subject experiences symptoms of serotonin syndrome, such as mental status changes, autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), and/or neuromuscular aberrations (e.g., hyperreflexia, incoordination).

**Blood count changes.** Blood test abnormalities that have been reported with the use of lorcaserin include decreases in lymphocyte counts and in hemoglobin. In clinical trials of at least 1-year duration, lymphocyte counts were below the lower limit of normal in 12.2% of patients taking the drug, compared with 9.0% of placebo patients. Hemoglobin was below the lower limit of normal in 10.4% of patients taking the drug, compared with 9.3% of placebo patients. During this study, participant will have regular CBC checks to monitor for any changes. The study physician will make a clinical decision as to the whether lorcaserin should be discontinued in any subjects who experience blood test abnormalities.

**Prolactin elevation.** Prolactin levels were found to be higher in lorcaserin than placebo patients. Lorcaserin moderately elevates prolactin levels. In a subset of placebo controlled clinical trials of at least one year in duration, elevations of prolactin greater than the upper limit of normal, two times the upper limit of normal, and five times the upper limit of normal, measured both before and 2 hours after dosing, occurred in 6.7%, 1.7%, and 0.1% of lorcaserin-treated patients and 4.8%, 0.8%, and 0.0% of placebo-treated patients, respectively. Participants will be advised to contact their PCP if they have symptoms of prolactin excess (breast enlargement and tenderness or milk discharge from the breast). The study physician/nurse practitioner will make a clinical decision as to whether lorcaserin should be discontinued in any subjects who experience symptoms of prolactin elevation.

**Psychiatric disorders.** Some drugs that target the central nervous system, including lorcaserin, have been associated with depression or thoughts of suicide. Events of euphoria, hallucination, and dissociation were seen with lorcaserin at supratherapeutic doses in short-term studies. In clinical trials of at least 1-year in duration, 6 patients (0.2%) treated with lorcaserin developed euphoria, as compared with 1 patient (<0.1%) treated with placebo. Doses of lorcaserin should not exceed 10 mg twice a day. Persons who have a history of suicide attempts or active suicidal thoughts should not take lorcaserin. Any subject who develops a psychiatric disorder such as euphoria, hallucination, dissociation, depression or thoughts of suicide will be instructed to discontinue lorcaserin and referred to their PCP for evaluation.

**Cognitive impairment.** Impairment in attention and memory, as well as confusion, sleepiness, and tiredness has been associated with lorcaserin. In clinical trials of at least one year in duration, impairments in attention and memory were reported adverse reactions associated with 1.9% of patients treated with lorcaserin and 0.5% of patients treated with placebo, and led to discontinuation in 0.3% and 0.1% of these patients, respectively. Other reported adverse reactions associated with lorcaserin in clinical trials included confusion, somnolence, and fatigue. Participants will be advised to use caution when operating machinery, including cars, until they are certain that the medication is not affecting them adversely. If subjects experience cognitive

impairment that does not improve and/or is severe, the study physician will evaluate whether the subject should be discontinued from lorcaserin.

**Valvular heart disease.** The use of lorcaserin may be associated with valvular heart disease, In clinical trials of 1-year duration, 2.4% of patients receiving lorcaserin and 2% of patients receiving placebo developed valvular regurgitation at 1 year. Participants will be advised to seek medical attention if they experience any symptoms of shortness of breath or leg swelling. Subjects found to have valvular heart disease after starting lorcaserin will be discontinued from the drug.

**Priapism.** Priapism (painful erections greater than 6 hours in duration) is a potential effect of 5-HT<sub>2C</sub> receptor agonism. In clinical trials, priapism occurred 0.1% in subjects taking lorcaserin compared to 0.1% in placebo-treated subjects. There is limited experience with the combination of lorcaserin and medication indicated for erectile dysfunction (ED). In this study, men taking medications for ED will be excluded. Subjects who have an erection lasting longer than 4 hours, whether painful or not, will be advised to immediately seek emergency medical attention and to discontinue lorcaserin.

**Reproductive risks.** The use of lorcaserin may pose risks to pregnancy and/or an unborn baby. Therefore, participants are advised not to get pregnant while in the study. And women of child bearing potential will be required to follow a study-approved method of birth control while participating in the study. Adequate birth control in this study is the use of double barrier methods (condom with spermicide or diaphragm with spermicide), stable hormonal contraception, intrauterine device, abstinence, or tubal ligation. In addition, the study medication may have unknown risks to breast-fed babies. Therefore, study participants are instructed not to breastfeed while taking the study drug. Should a female subject become pregnant while in the study, she will be discontinued from lorcaserin and the weight loss intervention. The subject will be asked to report the outcome of the pregnancy to the study staff (e.g. termination, birth outcome).

**Unforeseen risks.** Such risks include allergic reactions to medications. In addition, there may be other risks associated with lorcaserin that have not been identified. If additional risks are identified during the study, study participants will be informed about these risks by the study team.

## 7. STATISTICAL ANALYSIS

**Power analysis.** There are two primary intention-to-treat (ITT) contrasts based on a longitudinal data analysis design (weight measurements at 0, 24, and 52 weeks). The primary endpoint is change in body weight (in kg), as measured from randomization to week 52. The co-primary endpoint is the percentage of participants in the two groups that, at week 52, maintained the  $\geq 5\%$  reduction in body weight achieved during the 14-week group lifestyle modification program.

We predict a difference in weight change between the two groups (from randomization to month 12) of 3 kg (SD=5.0, ICC=0.80). We anticipate mean weight changes at week 52 of "0" kg for lorcaserin and "+3" kg for placebo. (This is a conservative prediction; we believe that lorcaserin

treated participants may lose a mean of 1-2 kg, while those treated by placebo may gain 4-5 kg. Estimates of mean weight regain for placebo-treated participants are based on prior studies we and others have conducted, while estimates for lorcaserin are based on findings from studies of sibutramine and liraglutide that have used similar run-in designs.) Furthermore, we predict that 80% of the lorcaserin participants will have maintained the  $\geq 5\%$  reduction in body weight from randomization through the 52 week assessment, as compared to only 50% of the placebo group. Based on the Holm's procedure that adjusts for multiple comparisons,<sup>37</sup> the smaller of the two p values resulting from analyses of our two primary contrasts will be compared at alpha equal to 0.025 and, if significant, the other contrast will be evaluated at 0.05. Consistent with this form of Type I error control, our primary approach for estimating study power is "the probability of at least one significant contrast."

Using a sample size equation for longitudinal clustered samples,<sup>38</sup> a randomization sample size of 68 participants in placebo and 68 participants in the lorcaserin treatment group (total sample: 136) provides over 80% power to detect the two primary contrasts to be statistically significant at the Holm's adjusted alpha levels noted above. This estimate allows for 20% attrition during the 52-week randomized trial, resulting in approximately 54 treatment completers in arm. The ITT longitudinal statistical design will further improve power by allowing the inclusion of available data for non-completers and the adjustment of possible variance reducing baseline covariates. All secondary analyses will be considered exploratory and evaluated at the alpha = 0.05 level. The power analysis was conducted using PASS 11.<sup>39</sup>

**Statistical plan: preliminary analyses.** All data will first be assessed by the data management staff, for missing data and out-of-range values with basic statistical procedures such as univariate statistics (i.e., means, standard deviations, ranges, frequencies, proportions, percentiles) and graphs, such as histograms, box and whisker plots, scatter plots and Q-Q plots. In addition, plots will be produced of individual and average trajectories of all repeated measures over time according to assigned treatment. All questions of data quality and integrity will be investigated before any statistical modeling is conducted.

Next, a preliminary analysis of all outcome and baseline demographic variables will be performed to test for differences in baseline measures between the randomized groups. The test of the adequacy of randomization will consist of tests of differences between the treatment conditions to see if the baseline variables are equally distributed between them. These baseline comparisons will be based on: t-tests or Wilcoxon rank sum tests for continuous variables, depending on the symmetry of the distributions; on Chi-square, Fisher's Exact or logistic regression for binary or ordinal variables; and on Poisson log-linear regression for count data. If imbalances are found at baseline, then the relevant variables will be treated as confounders in the post study analyses.

**Primary analysis.** To test the principal hypothesis that patients randomized to lorcaserin (with lifestyle intervention) will achieve significantly better maintenance of lost weight than those assigned to placebo (with lifestyle intervention, as measured by weight change (in kg) from randomization to week 52, a nested (cluster) mixed model will be fit utilizing the mixed procedure in the statistical software package SAS, version 9.3. An intention-to-treat (ITT)

analysis will fit an unstructured covariance matrix to adjust of the repeated measures data clustered with the individual participant. In addition, these models will contain the following fixed effects: main effect for change from baseline to each follow-up visit (weeks 24 and 52), group (2 conditions assuming intent-to-treat analyses), and interaction between the visit and group indicator variables. Tests of these interactions will correspond to tests of ITT differences among the treatment conditions. Estimates and confidence intervals for these group differences will be derived from interaction and main effects parameters of the models. The primary focus will be on the 52 week comparison. For the co-primary comparison of the percentage of participants in the two groups that, at week 52, maintained the  $\geq 5\%$  reduction in body weight achieved during the 14-week group lifestyle modification program, we will use generalized estimating equations (GEE) within the GENMOD procedure in SAS (2011) to fit population-averaged logistic models assuming the binomial distribution. As noted previously, we will use the Holm's procedure to control the overall alpha for the two sets of comparisons (for the continuous and dichotomous outcomes).

All randomized participants will be included in the primary intention-to-treat (ITT) analysis. A modified ITT analysis also will be conducted which includes only those participants who receive at least one dose of medication and provide at least one post-randomization measurement of body weight. A per protocol analysis will be conducted that includes only those participants who provide a measurement of body weight at week 52 (with a window of  $\pm 4$  weeks). All randomized participants will be included in the safety analysis. No interim analyses are planned (in order to maintain full power for the end-of-study comparisons).

**Secondary analyses.** Similar analytic strategies will be employed for all other continuous secondary efficacy endpoints, as well as for binary (dichotomous outcomes; i.e., percentage of participants who achieve different criterion weight losses). For the logistic model, differences will be presented as odds ratios with confidence intervals; for linear model, the least squares means and standard errors will be presented with confidence intervals.

**Missing data.** All analyses will be conducted using the ITT principle, in which all available data on all randomized patients are included. This approach minimizes bias if participants drop out of the intervention for different reasons. Assuming adequate fit of the mixed effects models to the data, the proposed nested random effects models are the most robust to missing data assumptions among standard longitudinal models that analyze all subjects regardless of how many post-randomization visits are missed. The following missing or unbalanced data scenarios can be accommodated by such models: attrition (drop out), missed interim visits, and missing covariate data where a subject is interviewed but data are missing on covariates of interest. All three types of missing data are handled by way of maximum likelihood under the proposed mixed effects models and the missing at random assumption (MAR). Therefore, we will explore the potential bias of missing data by comparing completers and non-completers to see if they differ systematically on values of non-missing variables. There are many ways to assess the assumption of MAR. We will consider imputing missing endpoint data using multiple imputation techniques, fitting selection models (e.g. MNAR), and fitting pattern mixture models.

## 8. SAFETY AND ADVERSE EVENTS

At each contact with participants, the study personnel will seek information on adverse events by specific questioning and, as appropriate, by physical examination. Information on all adverse events will be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results will be recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period will be recorded. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation will be recorded and reported immediately. All serious adverse events will be reported to the IRB within 10 working days.

## 10. DATA HANDLING AND RECORD KEEPING

Information about study participants will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- Protected health information (PHI) collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of research participants to revoke their authorization for use of their PHI
- View of PHI will be limited to individuals at the University of Pennsylvania directly involved in the study. The company donating the study product will not have access to PHI.

In the event that a participant revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For participants who have revoked authorization to collect or use PHI, attempts will be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

## 11. STUDY MONITORING, AUDITING, AND INSPECTING

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data, etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).



Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

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